F ENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 10 November 2000 (10.11.00)	
International application No. PCT/EP00/02194	**Applicant's or agent's file reference** CV-0290 PCT
International filing date (day/month/year) 13 March 2000 (13.03.00)	**Priority date** (day/month/year) 12 March 1999 (12.03.99)
Applicant PARSONS, Dave et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 October 2000 (06.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Zakaria EL KHODARY

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
CV-0290 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 02194	13/03/2000	12/03/1999
Applicant		
BRISTOL-MYERS SQUIBB COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. --

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

[redacted]ional Application No
PCT/EP 00/02194

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N59/12 A61L15/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 65538 A (OXIBIO INC) 23 December 1999 (1999-12-23) abstract page 9, last paragraph page 11, paragraph 2 page 16, last paragraph -page 17, paragraph 2 ---	1-4
X	US 5 128 136 A (BENTLEY J PETER ET AL) 7 July 1992 (1992-07-07) claims 6-9 ---	1-4
X	GB 2 276 546 A (DIVERSEY CORP) 5 October 1994 (1994-10-05) cited in the application claims 1,2 --- -/--	1,2,4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 July 2000	28/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Decorte, D

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Form PCT/ISA/210 (second sheet) (July 1992)

MATHYS & SQUIRE
INTELLECTUAL PROPERTY

100 GRAY'S INN ROAD LONDON WC1X 8AL
Tel +44 (0)20 7830 0000 Fax +44 (0)20 7830 0001
mail@mathys-squire.com www.mathys-squire.com

European Patent Attorneys
Chartered Patent Attorneys
European Trade Mark Attorneys
Registered Trade Mark Agents

S D RITTER MA (Cantab) MSc EPA CPA
P D GARRATT MA (Oxon) EPA CPA
M C MOIR BSc CEng EPA CPA MITMA
P D COZENS MA (Cantab) PhD EPA CPA
G W SCHLICH MA (Cantab) EPA CPA
I KAZI MA (Cantab) EPA CPA
S G COLMER BA (Cantab) EPA CPA
M J ARNOTT BA MITMA
H V J ADAMS MBiochem (Oxon) EPA CPA
A S BOOTH BA (Oxon) DPhil EPA CPA
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B V INGRAM CPhys EPA CPA
M R MACLEAN BSc MSc PhD EPA
E A SIMONS MA (Cantab) EPA CPA
A M TWITCHEN MITMA

International Preliminary Examining Authority
European Patent Office
Directorate General 2
D-80298 Munich
Germany

COPY

Our Ref: SGC/23080
Your Ref: -

4 June 2001

Dear Sirs

International Patent Application No. PCT/EP00/02194
Bristol-Myers Squibb Company

This letter is in response to the first written opinion dated 29 December 2000. The International Division is thanked for the grant of extensions.

AMENDMENT

I file herewith, in triplicate, revised claims. The Examiner is requested to replace the claims currently on file by the revised claims. Claim 1 is unchanged; claim 4 becomes revised claim 2. Revised claim 3 has support at page 4, lines 6 to 7 while revised claim 4 has support in Example 1 and at page 4, line 9. Revised claim 5 has support on page 4, line 6 while claims 6 to 8 inclusive are use claims based on original claims 2 and 3.

For the Examiner's convenience, and as requested, a manuscript amended version of the original claims is attached.

THE CITED ART

WO99/65538 is an intervening publication and will be dealt with, as appropriate, in the national and regional jurisdictions.

US 5128136 relates to a collagen gel. The collagen gel is both stabilised and sterilised with iodine. The iodine may be generated, from a point-of-use kit, from iodide, iodate and buffer at a low pH of ca. 3.4 which ensures rapid iodine release. However, on mixing with the collagen, the pH is rendered neutral (i.e 7.0) (at '136, column 7, lines 40 to 46). At no point is the pH of the composition **maintained between 4.5 and 6 so that iodine is generated at a physiologically acceptable dose and rate**. It is noted that it is the stabilised gel, and not its stabilising composition, which is used to treat the wound.

/Cont'd...

In conclusion, this document does not anticipate the present invention as claimed.

GB 2276546 is discussed in some detail in the present specification at page 2, line 19 to page 3, line 8. As noted, the primary aim of this disclosure is to produce a disinfectant bovine teat dip and, while the composition is constituted at the point-of-use, the pH generated is very low. Thus, in Example 1 it is about 3.5, in Example 2 from 3.5 to 4.0; in Example 3 from 3.5 to 4.0; Example 4 is said to be substantially identical to Example 3; the initial pHs quoted in Example 5 are between 3.8 and 3.95; the pHs quoted in Example 6 are between 3.2 and 3.4 with the advice (at '546, page 13, lines 27 and 28) that the pH should not be below pH3.

In conclusion, not only does this document not disclose a pH between 4.5 to 6.0 as is required in claim 1 but also, by utilising a lower pH, results in rapid release of iodine suitable for general disinfectant use but quite unsuitable for use in wounds. This document cannot, therefore, anticipate any of the present claims.

US 4271149 discloses a disinfectant composition in which the iodine source, oxidant and buffer are **all stored together in admixture**, its intention being to increase storage stability (at '149, col. 1, lines 13 and 14). The levels of iodine in such compositions are too high for use in wounds, for the reasons mentioned on page 1 of the present specification.

WO 95/12316 discloses a sterilising solution for surgical instruments. It is clear that again all of the components are **stored together in admixture** (at '316, page 4, lines 20 to 25). Furthermore, while a maximum pH of 5 is disclosed, the actual pH is 4.0 or 4.5.

In conclusion, none of the citations deprives the invention as now claimed of novelty.

As to inventive step, the compositions of the present invention consist of two (or more) separate components which when mixed at the point of application, for example, via a static mixer applicator, contain sufficient reactants to generate levels of iodine over a sustained period at levels that have efficacy but are non-toxic to human tissue.

In summary, the present application discloses a highly controlled chemistry for use as an efficacious but non-toxic antimicrobial agent in wounds. None of the cited patents specifically address this issue.

The present claims are thus novel, possess an inventive step and are industrially applicable.

Yours faithfully

Colmer, Stephen Gary
MATHYS & SQUIRE
Enc: Replacement claims in triplicate; manuscript amended claims /ms

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COLMER, Stephen Gary
MATHYS & SQUIRE
100 Grays Inn Road
LONDON WC1X 8AL
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.06.2001
Applicant's or agent's file reference CV-0290 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/02194	13/03/2000	12/03/1999

Applicant
BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Gallego, A Tel.+49 89 2399-8102

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
CV-0290 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/02194	13/03/2000	12/03/1999
International Patent Classification (IPC) or national classification and IPC A01N59/12		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/10/2000	18.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Boletti-Cremers, K Telephone No. +49 89 2399 8541

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/02194

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-7	as originally filed	

Claims, No.:

1-8	with telefax of	04/06/2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 6-8.

because:

☒ the said international application, or the said claims Nos. 6-8 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-5

No: Claims 6-8

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

POINT I.

In view of the fact that example 1 says that the PH of the composition disclosed there is *about* 5,4 and not 5,4 "per se", as presently drafted , claim 4 , which is meant to possess a support on p.4 line 9 and example 1 , encompasses a specific teaching which was not part of the original disclosure and said claim is therefore not acceptable under Rule 70.2(c) PCT.

POINT III.

For the assessment of the presently worded claims 6-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable claims to the **use of a compound or a composition in medical treatment**, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a new medical treatment.
In this respect , the IPEA wishes to point out that claim 6 is allowable under the requirements of the EPO.

POINTS V and VI.

The following documents , quoted in the I.S.R., have been considered as relevant for the examination of the present application . Their numbering will be adhered to for the rest of the procedure.

(1) WO-A- 99 65538.
(2) US-A-5 128 136.
(3) GB-A-2 276 546 , cited in the application.
(4) US-A-4 271 149.
(5) WO-A-95 12316.

Novelty.

1. Although (1) is not prior art according to the Chap II PCT proceedings, its content will

affect the novelty of the claimed matter in the regional European proceedings to come.

Moreover , the extensive examination of that document , on the question whether it constitutes prior art or not , will depend essentially on the analysis of the validity of the claimed priority rights of present application and will only be performed in the regional European proceedings to come .

2. In view of the fact that (2) discloses a collagen-gel which uses a substantially neutral PH at the point to mix the collagen with the iodine (see (1) column 7 , lines 40-46) , the novelty of the claimed matter with respect to the content of (1) can be acknowledged .

3. In view of the fact that (3) refers to compositions where, after final mixing of the ingredients , the PH is between 3.2 and 4 (see the examples of (3)), the novelty with respect to the content of (3) can also be acknowledged .

4. In view of the fact that the mixtures disclosed in (4) are not held separately before the moment (and point) of use , novelty with respect to the content of (4) can also be acknowledged , despite the fact that the PH used for the compositions of (4) is said to be optimised at 5,5-6,5 (see column 5 , lines 1-2) and that the final iodine content is of an overlapping range(see column 2 , lines 43-49 of (4))

5. The same conclusions as for (4) can be drawn from the content of (5) which also discloses compositions stored together in admixture at a maximum PH of 5.

Inventive step.

In view of the most relevant prior art , namely (3) , present application deals the problem to provide alternative topical antimicrobial compositions which avoid at the same time wound and skin irritation and retardation of wound healing.
In other words , the claimed composition should contain sufficient reactants to generate levels of iodine over a sustained period and that they would be less toxic to humans tissues .
Insofar as the solution of that problem is merely characterised by the instant 2 parts

compositions on file , compositions which differ merely from the 2 parts compositions disclosed in (3) by means of the use of a higher PH and insofar as that the content of (4) and (5) provide evidence that the increase of the PH enables iodine to be produced at a very slow speed (see (4) , column 2, lines 31-43), presently claimed matter is considered to be the result of the obvious combinations of the teachings of the most relevant prior art (3) , with (4) and (5) because the longer lasting effect of the claimed compositions is implicitly suggested by the content of (4) and (5) .
At the entry of the application into the regional phase , the Applicant will be therefore invited to show by argumentation or technical evidence , that the claimed compositions on file possess an advantage(for instance a lower toxicity) or a surprising feature when they are compared with the compositions of (3) in order to enable the acknowledgment of the inventive step of the claimed matter on file .

POINT VII.

(a) Documents (2) (4) and (5) and possibly (1), should be quoted and briefly commented in the description in the regional proceedings .

CLAIMS:

1. An iodine preparation composition suitable for use on wounds comprising an iodine source, and oxidant and a buffer characterised in that the iodine is held separately from the oxidant until the point of use, and that the buffer is capable of maintaining the pH of the composition at between pH 4.5 and pH 6 so that iodine is generated at a physiologically acceptable dose and rate.

2. An iodine preparation composition as claimed in claim 1 characterised in that the composition is capable of generating from 5µg of iodine per g of composition per hour to 1500µg of iodine per g of composition per hour, preferably 100µg of iodine per g of composition per hour.

3. An iodine composition as claimed in claim 2 formulated to generate the said levels of iodine over a period of three days.

4. An iodine composition according to any preceding claim wherein the pH of the composition is maintained between 5.4 and 5.8.

5. An iodine composition according to any preceding claim which includes from 0.2% to 2% by weight of iodine.

6. The use of an iodine preparation composition according to any preceding claim for the manufacture of a medicament for use on wounds.

7. Use of an iodine preparation composition according to any preceding claim for the treatment of wounds.

8. Use according to claim 6 or 7 for the treatment of sepsis in wounds.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A01N 59/12, A61L 15/44

A1

(11) International Publication Number: WO 00/54593

(43) International Publication Date: 21 September 2000 (21.09.00)

(21) International Application Number: PCT/EP00/02194

(22) International Filing Date: 13 March 2000 (13.03.00)

(30) Priority Data:
9905663.2 12 March 1999 (12.03.99) GB

(71) Applicant *(for all designated States except US)*: BRISTOL-MYERS SQUIBB COMPANY [US/US]; 345 Park Avenue, New York, NY 10154 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: PARSONS, Dave [GB/GB]; 6 Briar Drive, Heswell, Wirral L60 5RN (GB). JACQUES, Elizabeth [GB/GB]; 9 Cedar Grove, Hoole, Chester CH2 3LQ (GB). BOWLER, Philip [GB/GB]; 8 Woodbridge Close, Appleton, Warrington, Cheshire WA4 5RD (GB).

(74) Agent: MAYS, Julie; Bristol-Myers Company Limited, Patent Dept., Swakeleys House, Milton Road, Ickenham, Uxbridge UB10 8NS (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IODINE PREPARATION COMPOSITON

(57) Abstract

An iodine preparation composition suitable for use on wounds comprising an iodide source, an oxidant and a buffer characterised in that the iodide is held separately from the oxidant until the point of use, and that the buffer is capable of maintaining the pH of the composition at between pH 4.5 and pH 6 so that iodine is generated at a physiologically acceptable dose rate.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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Iodine Preparation Composition

This invention relates to an antimicrobial composition which can be applied to wounds, cuts, abrasions or burns for the prevention or treatment of infections. More particularly the invention relates to a composition capable of providing effective antimicrobial activity while at the same time avoiding wound and skin irritation and retardation of wound healing.

Topical antimicrobial materials and preparations containing them have long been recognised as important parts of antisepsis of intact skin and wounds. Iodine has been recognized as an antimicrobial agent with effectiveness against a wide range of micro-organisms. There are however several barriers to making an effective antimicrobial composition for application to wounds based on iodine. One problem is that iodine tends to react with organic materials found in the wound other than the intended microbial targets. This means that to be effective, iodine needs to be included at high levels such as 0.9% by weight, as described in "Handbook of Wound Dressings" edited by Stephen Thomas, 1994 Journal of Wound Care. . At such levels and with continued use iodine may have undesirable local side effects such as cell toxicity, hypersensitivity reactions, skin staining, and unpleasant odour and systemic adverse effects such as metabolic acidosis and impairment of renal function. For this reason application of iodine is recommended at levels below 1.35g in one week.

A further problem is that iodine has a relatively short shelf life when in aqueous solution meaning either that compositions which include water need to be freshly prepared before each application or again that iodine is included at high levels. These factors limit product form.

In the past these problems with iodine have sought to be addressed by the use of iodophors which act as a release mechanism for iodine. Iodophors are readily dissociable, loose complexes of iodine with polymers or surfactants. Iodophor compositions are not best suited to use on wounds because when applied to a wound, all iodine present in the composition is readily available for reaction and therefore the adverse reactions associated with high levels of iodine are not necessarily avoided.

There thus exists a need for a composition which delivers iodine to a wound at a rate which is high enough to provide effective antisepsis but which is low enough
to avoid the problems of adverse reactions associated with high levels of iodine.

GB-B-2276546 to Diversey relates to improved iodophors which are prepared at the point of use. The composition comprises an iodide source, an oxidant and an acid source, the oxidant becoming active only when the composition is dissolved in an aqueous medium. The composition is said to overcome the stability problems associated with producing teat dip/spray iodine formulations for use in

the control of bovine mastitis. The rate of generation of iodine needed for these topical formulations for use on intact skin far exceeds that tolerable to a wound. In these compositions such high levels of iodine are generated that a hydrotrope must be included to prevent the iodine from crystallising. In addition, iodine has a complex chemistry in aqueous solutions and exists in a number of equilibria. At high iodine concentrations in the presence of iodide there is a strong tendency for the tri-iodide ion to form. We believe that this ion has very little antimicrobial activity but can still be absorbed with the risk of systemic toxicity.

We have found that it is possible to prepare a composition which is capable of generating iodine at a rate and level that makes it suitable for use in wounds. This is achieved by separating certain of the ingredients and controlling the kinetics of the generation of iodine through the manipulation of pH.

Accordingly the present invention provides an iodine preparation composition suitable for use on wounds comprising an iodide source, an oxidant and a buffer characterised in that the oxidant is held separately from the iodide until the point of use, and that the buffer is capable of maintaining the pH of the composition at between pH 4.5 and pH 6 so that iodine is generated at a physiologically acceptable and efficacious rate.

The invention allows the preparation of compositions generating a low but effective iodine level for example up to about 2000μg per g of composition per

hour, preferably in the range of 5μg per g of composition per hour to 1500μg per g of composition per hour, more preferably in the range 50μg per g of composition per hour to 1000μg per g of composition per hour so that the amount of free iodine available for antisepsis at any time is at least 0.001%.

The compositions of the invention are preferably formulated to generate the above levels of iodine over a period of about 3 days.

The pH of the composition of the invention is generally below 5.8. We have found that if the pH is greater than about 6, the rate of production of iodine by reaction of the oxidising agent with iodide ions is too low to balance any losses of iodine by reaction with the organic matter. We have found that it is generally desired that the pH of the compositions is not below about 4.5 as otherwise there is a danger that the rate of oxidation of the iodide ions will be too fast with the result that the composition could become toxic.

The desired pH of the compositions may be achieved by incorporating buffering agents therein. Examples of buffering agents which may be included are citric acid/disodium hydrogen phosphate, citric acid/sodium citrate, acetic acid/sodium acetate. The buffering agent may conveniently be present in an amount of about 2% to 10%, preferably about 4% to 6% by weight and particularly about 5% by weight so as to provide an isotonic composition.

The amount of oxidant in the composition is tailored to provide a stoichiometric match with iodide. Preferably the oxidant is iodate and is provided in a molar ratio of 1:5 with iodide. In this way the iodide present in the composition fully reacts with all the oxidant. To provide the levels and rate of production of iodine in the range described above it is desirable to include up to 2% by weight of iodide, preferably, from 0.2 % to 2 % by weight of iodide. Iodide and iodate are preferably present as sodium salts although other usual counter ions may be used.

Convenient forms of administration of the composition include aqueous gels, films, creams, tablets and capsules.

The following examples are illustrative of the present invention.

Example 1.

Gel A	Weight g
Hydroxyethyl cellulose	30.00
Propylene Glycol	150.00
Na_2HPO_4	35.61
Citric Acid	21.01
Potassium Iodate	1.124
Water	762.256

Gel B	Weight in g

Hydroxyethyl cellulose	30.0
Propylene Glycol	150.0
Potassium Iodide	4.36
Water	815.64

Gel A was made by dissolving the buffer salt in a water/propylene glycol mix and then adding the iodate. When the solution is clear the hydroxyethyl cellulose is added and mixed until gelation is complete. Gel B was made by dissolving iodide in a water/propylene glycol mix. Hydroxyethyl cellulose was added to this mixture and mixed until gelation was complete.

The gels were packaged in separate syringes which were bound together with their nozzles fitted into a Y-shaped connecter. The contents were sterilised by autoclaving at 121 C for 15 minutes. Simultaneous depression of the plungers allows the gels to be co-extruded and allows the gels to react while being dispensed into a wound. The co-extrusion of the gels results in a product producing approximately 100µg per g of composition per hour at a pH of about 5.4. The composition generated a greater than 5 log kill of *S. aureous* (NCIMB 9518) which is regarded as being an acceptable level of antimicrobial activity.

Example 2

Film A g

Hydroxypropylcellulose	16
Propylene Glycol	4
Potassium Iodate	0.1124
Sodium phosphate	1.7805
Citric acid	1.0505
Water	77.0566

Film B

Hydroxypropylcellulose	16
Propylene Glycol	4
Potassium Iodide	0.436
Water	79.564

The films are produced by knife over roller coating of aqueous solution onto an inert carrier followed by drying at a temperature not exceeding 100 C and sterilised by gamma irradiation.

The films may be cut into rectangles and added to a wound whereupon they dissolve in the wound fluid and reaction takes place.

Claims

1. An iodine preparation composition suitable for use on wounds comprising an iodide source, and oxidant and a buffer characterised in that the iodide is held separately from the oxidant until the point of use, and that the buffer is capable of maintaining the pH of the composition at between pH 4.5 and pH 6 so that iodine is generated at a physiologically acceptable dose and rate.

2. An iodine preparation composition suitable for use on wounds comprising an iodide source, an oxidant and a buffer for simultaneous or sequential use in the treatment of sepsis in wounds.

3. Use of an iodine preparation composition comprising an iodide source, an oxidant and a buffer for simultaneous or sequential use in the treatment of sepsis in wounds.

4. An iodine preparation composition as claimed in claim 1 characterised in that the composition is capable of generating from 5µg of iodine per g of composition per hour to 1500µg of iodine per g of composition per hour, preferably 100µg of iodine per g of composition per hour.

INTERNATIONAL SEARCH REPORT

Inter[illegible]nal Application No
PCT/EP 00/02194

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N59/12 A61L15/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 65538 A (OXIBIO INC) 23 December 1999 (1999-12-23) abstract page 9, last paragraph page 11, paragraph 2 page 16, last paragraph -page 17, paragraph 2 ---	1-4
X	US 5 128 136 A (BENTLEY J PETER ET AL) 7 July 1992 (1992-07-07) claims 6-9 ---	1-4
X	GB 2 276 546 A (DIVERSEY CORP) 5 October 1994 (1994-10-05) cited in the application claims 1,2 --- -/--	1,2,4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
20 July 2000	28/07/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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